

### **REMARKS**

Upon entry of the present amendment, claims 1-12, 14 and 16-51 are pending in the instant application. Applicants note that Office Action Summary in the Office Action mailed October 6, 2004 erroneously listed the pending claims as “claims 1-44”. However, during the prosecution of the corresponding PCT application (PCT/IB00/01076), Applicants filed Article 19 Amendments that included claims 1-51. A copy of these Article 19 Amendments was provided at the time instant application was filed. Applicants submit herewith a copy of the Transmittal to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 U.S.C. 371 (2 pages) listing, in Item 7, the submission of “Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))”. Applicants have also provided a copy of the return postcard listing “Amendments to the claims of the International Application under PCT Article 19”, which was stamped “JC14 Rec’d PCT/PTO 18 Jan 2002”. Thus, Applicants submit that the pending claims as of the date of the instant Office Action included claims 1-51, not claims 1-44.

In the instant Amendment, claims 1, 4, 5, 7, 8, 11, 16, 17, 20, 24, 25, 27, 28, 36-38 and 47 have been amended. In particular, claims 1, 11 and 20 have been amended to recite complex skin equivalents. Support for these amendments is found, for example, at least at page 4, lines 12-14. Claims 4, 5, 7, 8, 16, 17, 24, 25, 27, 28 and 36-38 have been amended to maintain proper antecedent basis in light of the amendments to claims 1, 11 and 20. In addition, claim 11 has been amended to remove the term “preferably”, claim 47 has been amended to depend from claim 1, and claims 13 and 15 have been cancelled without prejudice or disclaimer. Accordingly, the amended claims are fully supported by the specification and claims as originally filed, and no new matter has been added by these amendments.

#### **Claim rejections under 35 U.S.C. §103(a)**

Claims 1-4, 7-12, 14, 16-24, 27-34 and 36 have been rejected under 35 U.S.C. § 103(a), as obvious in view of U.S. Patent No. 5,968,546 to Baur *et al.* (“Baur”), in combination with Lenoir *et al.*, 130 DEV. BIOL. 610 (1988) (“Lenoir”) and Lenoir-Viale *et al.*, 285 ARCH. DERMATOL. RES. 197 (1993) (“Lenoir-Viale”).

The Examiner has acknowledged that Baur teaches “that the plucked hair is not cultured in the state in which it exists immediately after plucking from the skin but instead is subject to

dissection and the hair bulb and infundibular parts are removed and the follicles are subsequently cultured. (See Office Action at pages 2). Thus, Baur requires further dissection of the hair follicle prior to culturing.

However, the Examiner has concluded that Lenoir and Lenoir-Viale describe the production of equivalents from human hair follicles, wherein the removal of the bulb is merely a matter of convenience:

Applicants merely state at page 3 of the specification that the standard methodology of a “tedious and time-consuming dissection of the plucked anagenic hair was not required.” As evidenced by the disclosure of Lenoir et al. and Lenoir-Viale et al., the preparation of the plucked follicle by cutting off the soft end bulb and then cutting the follicle into pieces is not the same as the “a tedious and time-consuming dissection of the plucked anagenic hair” yet produces an epidermal equivalent. Clearly, the dissection of Baur is not critical to the production of the epidermal equivalent of Baur. (Office Action, at page 3)

According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to culture the intact hair follicle immediately after plucking since “Lenoir et al. and Lenoir-Viale et al. remove the bulb for matters of convenience rather than criticality to the production of the equivalent.” (See Office Action at pages 3-4).

The pending claims are directed to methods for the treatment of a skin defect. The methods recited by claims 1, 11 and 20 and their respective dependent claims (including claims 2-4, 7-10, 12, 14, 16-19, 21-24 and 27) include the steps of (i) culturing an intact hair follicle of an anagenic hair to obtain outer root sheath cells; (ii) culturing the outer root sheath cells to obtain keratinocyte precursor cells; (iii) preparing an epidermal or dermal equivalent that includes the keratinocyte precursor cells; and (iv) applying at least a portion of the epidermal or dermal equivalent to the skin defect. The methods recited by claim 28 and its dependent claims (including claims 29-34 and 36) include the steps of (i) plucking an anagenic hair; (ii) primary-culturing the keratinocyte precursor cells by adhering the anagenic hair, *in toto*, to a microporous membrane having growth-arrested/limited feeder cells on its undersurface; (iii) organotypically-culturing the outer root sheath cells harvested from the primary cultures by inoculating a microporous membrane also having growth-arrested/limited feeder cells on its undersurface; (iv) generating an epidermal or complex skin equivalent for subsequent use as a graft insert; and (v) contacting the epidermal or skin equivalent with a skin defect and immobilizing the equivalent at the site of contact.

Thus, the methods recited by the pending claims culture intact, plucked hair follicles to generate epidermal or skin equivalents for use in healing skin defects. However, Applicants contend that Baur, Lenoir, and Lenoir-Viale, alone or in combination, fail to disclose or suggest culturing an intact hair follicle.

As described above, the Examiner has acknowledged that Baur requires further dissection of the hair follicle prior to culturing. Lenoir fails to remedy the deficiencies in the teachings of Baur. The Lenoir method for culturing the anagenic hair follicles is described at page 612, second column, lines 20-25:

As an attempt to grow these epithelial cells, hair follicles were *cut into pieces*, and the upper and lower halves were implanted into dermal equivalents and cultured for 5 days under immersion (*see Materials and Methods*). (emphasis added)

Thus, this passage explicitly refers the reader back to the Material and Methods section of Lenoir, which describes, at page 661, first column, lines 14-19, that “the bulbs were removed with scissors, since their soft end would hamper the implantation of the explant into the collagen gel.” Similarly, the Materials and Methods section of Lenoir also teaches that the hair follicles were cut into pieces “in order to reduce the size of the explant to ensure that it could keep its upright position.” (Lenoir, at page 611, column 1). Accordingly, contrary to the Examiner’s contention, the Lenoir methods do not use *intact* hair follicles to create epidermal equivalents. Rather, the methods disclosed by Lenoir require further dissection of a plucked hair follicle by removing follicle bulbs with scissors and cutting the follicles into at least two pieces prior to implanting the follicles vertically into a dermal equivalent made of collagen gel. (*See Lenoir*, at 611, column 1). Thus, the stratified epithelium similar to epidermis observed in Lenoir was generated from a dissected hair follicle.

Therefore, contrary to the Examiner’s assertion, further dissection of the plucked hair follicle is not simply a matter of convenience for a researcher practicing the Lenoir method of creating dermal equivalents. Rather, further dissection is a necessary step in the Lenoir method. Prior to Applicants’ invention, further dissection of the hair follicle to remove the bulb and infundibular parts was the standard method of culturing outer root sheath cells from plucked hair follicles. (*See e.g.*, specification at page 3, lines 12-15). Applicants were the first to discover that dissection of the hair follicle after plucking was not necessary. (*See e.g.*, specification at page 2, lines 16-22). Accordingly, Lenoir fails to remedy the deficiencies in the teachings of

Baur, and, therefore, the combination of Lenoir and Baur does not render the pending claims obvious.

Moreover, the addition of Lenoir-Viale fails to remedy the deficiencies in the teachings of Lenoir and Baur, either alone or in combination. The methods of culturing anagenic hair follicles to create dermal equivalents disclosed by Lenoir-Viale require explantation of a plucked hair follicle onto a substrate of human dead de-epidermized dermis (DED). In addition, Lenoir-Viale teaches away from using other types of matrices or substrates in the disclosed dermal equivalents. For example, Lenoir-Viale teaches, at page 197, column 2, that a DED substrate is more resistant to mechanical stresses and less prone to collagenolysis than a collagen-based matrix.

Accordingly, Applicants contend that one of ordinary skill in the art would not have been motivated to modify the Lenoir-Viale dermal equivalents to include a non-DED substrate, such as, for example, the collagen gel matrix described by Lenoir, or the microporous membranes carrying human fibroblast feeder cells on their underside described by Baur.

Thus, for these reasons, the combined teachings of Baur, Lenoir and/or Lenoir-Viale fail to render the pending claims obvious. Therefore, this rejection should be withdrawn.

### **Objections Under 37 C.F.R. 1.75**

The Examiner has objected to claim 15 under 37 U.S.C. 1.75 as being a substantial duplicate of claim 13. Applicants note that claim 15 has been cancelled herein. Thus, any rejection of this claim has been rendered moot and should be withdrawn.

### **Double Patenting**

#### *Statutory-Type Double Patenting*

Claims 13 and 15 have been rejected under 35 U.S.C. §101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,548,058. Applicants note that claims 13 and 15 have been cancelled, thereby obviating any rejections of these claims. As such, this statutory-type double patenting rejection should be withdrawn.

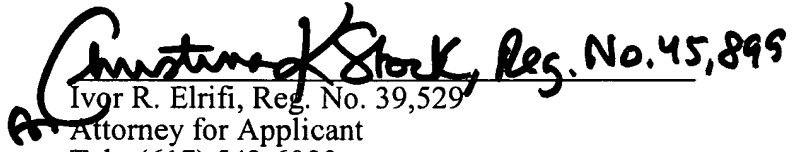
*Nonstatutory Double Patenting*

Claims 1-27 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,548,058, while claims 28-44 have been rejected under the judicially created doctrine of obviousness-type double patenting as being patentable over claims 1-15 of U.S. Patent No. 6,730,513. Applicants submit herewith a terminal disclaimer over U.S. Patent Nos. 6,548,058 and 6,730,513. Accordingly, Applicants request that the withdrawal of these double-patenting rejections.

### CONCLUSION

On the basis of the foregoing amendments and arguments, Applicant submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

  
Ivor R. Elrifi, Reg. No. 39,529  
Attorney for Applicant  
Tel: (617) 542-6000  
Fax: (617) 542-2241

Customer No. 30623